

Note

Analytical gas chromatographic separations of diastereomeric *tert.*-butylmethoxyphenylsilyl ethers

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Chiral acylating agents are extensively used for converting enantiomeric alcohols into diastereomeric esters suitable for analysis on achiral columns by gas-liquid chromatography (GLC). The analogous use of chiral silylation appears to be unreported, but would be of practical value [especially in GLC combined with mass spectrometry (MS)] if suitable reagents could be developed. Unfortunately, there are two major difficulties: many chiral silyl halides have limited optical stability, and the stereochemical course of nucleophilic displacements of the halide ions is far from uniform^{1,2}. Nevertheless, there are reported examples of silyl halides with moderate optical stability and of etherifications that proceed either with complete retention of configuration or with substantial inversion^{1–3}. Pending the design of reagents that would afford ethers without loss of stereochemical control, we have examined the extent of separation, by GLC, of diastereomeric *tert.*-butylmethoxyphenylsilyl (TBMPS) ethers of various alcohols. The chiral silane compound *tert.*-butylmethoxyphenylsilyl bromide (TBMPSBr), in racemic form, was introduced by Guindon *et al.*⁴ as a versatile protecting reagent for alcohols, yielding derivatives that are stable towards hydrolysis: the TBMPS ethers can, however, be selectively cleaved by tetrabutylammonium fluoride in the presence of other stable silyl ethers such as *tert.*-butyldimethylsilyl ethers. Under appropriate conditions, the formation of TBMPS ethers may be selective for primary hydroxyl groups², and this feature has been applied in the reported analysis of the arachidonic acid metabolite, 12,20-diHETE (a 12,20-dihydroxyeicosatetraenoic acid): the derived methyl 12,20-dihydroxyeicosanoate yielded a 12-trimethylsilyl, 20-TBMPS ether suitable for GLC-MS⁵.

EXPERIMENTAL

Gas chromatographic separations of four examples of diastereomeric silyl ethers containing chiral silicon have been reported earlier⁶.

TBMPS ethers were prepared from the secondary alcohols (100 μg) by reaction at 80°C, in a sealed vial, for 5 min, with TBMPSBr (Aldrich, Gillingham, Dorset, U.K.) [4 μl : 20–30 molar proportions (mol. prop.)] in a mixture of acetonitrile (20 μl) and dry pyridine (20 μl). The reagents were removed by evaporation under nitrogen, and the residual products extracted with cyclohexane and purified on a column (4 cm \times 1 cm I.D.) of silica gel 60 DCC (ICN Biomedicals: Park Scientific, Northampton, U.K.). The TBMPS ether of *trans,trans*- β -decalol was also purified by thin-layer chromatography (TLC) on silica gel 60 F₂₅₄ (Merck; BDH, Poole, U.K.): analytical TLC in the mobile phase chloroform–ethyl acetate (3:1, v/v) gave a single spot at R_F 0.69, and recovery from a preparative TLC plate gave the pure product in good yield as judged by GLC.

GLC was carried out with a Hewlett-Packard 5880 A instrument equipped with CP Sil5 CB and CP Sil19 CB fused-silica capillary columns (25 m \times 0.32 mm I.D.; Chrompack, London, U.K.) and dual flame ionisation detectors. Helium carrier-gas and make-up gas flow-rates were 3 and 25 ml/min, respectively. The column temperature programming conditions are presented in Figs. 1 and 2.

GLC–MS was performed with a Hewlett-Packard 5890 gas chromatograph interfaced to a VG 70-250S instrument. The column temperature programming conditions were similar to those presented in Figs. 1 and 2. Mass spectra (40 eV) were acquired using the following conditions: accelerating voltage, 8 kV; filament current, 4 A; trap current, 100 μA ; source and interface temperatures, 240 and 290°C, respectively.

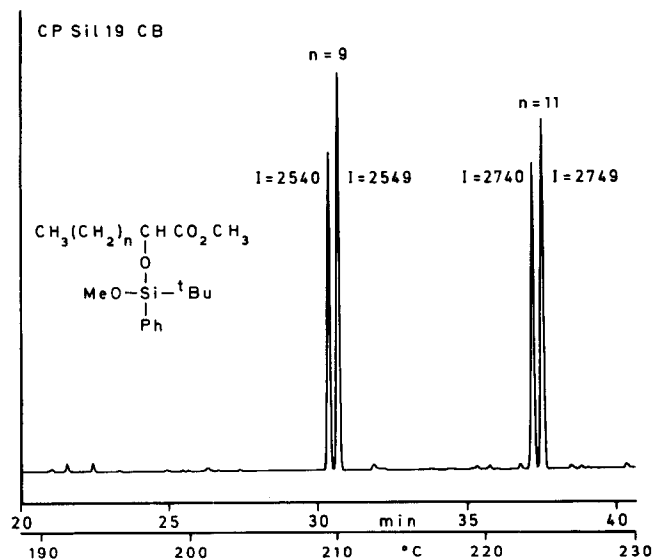


Fig. 1. Gas chromatographic separation of the TBMPS derivatives of (\pm)-methyl-2-hydroxy laurate ($n = 9$) and (\pm)-methyl-2-hydroxy myristate ($n = 11$). Column, CP Sil19 CB fused-silica capillary (25 m \times 0.32 mm I.D.; film thickness, 0.18 μm); column temperature, programmed from 80°C (2 min) to 160°C (1 min) at 30°C/min, and then at 2°C/min to 240°C; helium flow-rate, 3 ml/min. $\text{tBu} = \text{tert.}$ -Butyl; Me = methyl; Ph = phenyl.

RESULTS AND DISCUSSION

Fig. 1 shows the pairs of diastereomer peaks observed for TBMPS ethers of methyl 2-hydroxylaurate and methyl 2-hydroxymyristate. The retention index increments (ΔI) resulting from TBMPS ether formation were 788 and 782, respectively, on the CP Sil19 CB phase. In these examples, and in many others studied, the proportions of diastereomers formed were unequal, indicating a not unexpected stereoselectivity in the rates of etherification. As only the racemic forms of the silylation reagent and substrates were employed, no evidence has been obtained as to the stereochemical course of the displacement of bromide ion.

Derivatives of two isomeric racemic bicyclic alcohols, *trans,trans*- α -decalol and *cis,cis*- α -decalol, each afforded diastereomeric TBMPS ethers that were well separated, particularly on the more polar stationary phase CP Sil19 CB as shown in Fig. 2. Separations (as ΔI values) observed for the four decalols studied are cited in Table I.

The mass spectra [40 eV e.i. (electron impact)] of the derivatives cited in this note were dominated by ions of type $(M-57)^+$ (resulting from the loss of a *tert*-butyl radical from the molecular ion) and by several ions comprising reagent moieties. For example, the decalin TBMPS ethers yielded prominent ions at m/z 153, for which high-resolution MS indicated a mass of 153.0383 corresponding to $C_7H_9O_2Si$ as expected for the ion $(C_6H_5(OCH_3)SiOH)^+$. For the hydroxy-ester derivatives (Fig. 1) minor fragmentations involving losses of $MeO\cdot$ were also observed. The presence of other substituents capable of directing favourable cleavages (as exemplified in ref. 5) would afford mass spectra of a more structurally informative nature.

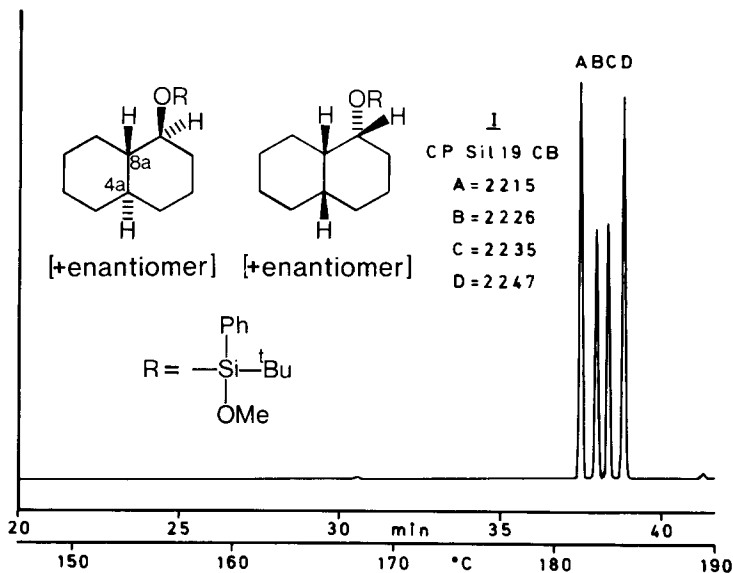


Fig. 2. Gas chromatographic separation of the TBMPS derivatives of (\pm)-*trans,trans*- α -decalol (A/B) and (\pm)-*cis,cis*- α -decalol (C/D). Column, CP Sil19 CB fused-silica capillary (25 m \times 0.52 mm I.D.; film thickness, 0.18 μ m); column temperature, programmed from 80°C (2 min) to 115°C (1 min) at 30°C/min, and then at 2°C/min to 190°C; helium flow-rate, 3 ml/min. 'Bu = *tert*-Butyl; Me = methyl; Ph = phenyl.

TABLE I
RETENTION INDEX DATA FOR TBMPS ETHERS OF (\pm)-DECALOLS

Decalols	CP Sil5 CB ^a		CP Sil19 CB ^b	
	I	ΔI	I	ΔI
<i>cis,cis</i> - α - (1 <i>RS</i> , 4 <i>aSR</i> , 8 <i>aSR</i>)	2122, 2132	10	2235, 2247	12
<i>trans,trans</i> - α - (1 <i>RS</i> , 4 <i>aSR</i> , 8 <i>aRS</i>)	2105, 2115	10	2215, 2226	11
<i>cis,cis</i> - β - (2 <i>RS</i> , 4 <i>aSR</i> , 8 <i>aRS</i>)	2146, 2150	4	2264, 2269	5
<i>trans,cis</i> - β - (2 <i>RS</i> , 4 <i>aRS</i> , 8 <i>aRS</i>)	2136, 2141	5	2244, 2249	5

^a A dimethylsiloxane polymer.

^b A siloxane copolymer containing 7% cyanopropyl, 7% phenyl, 85% methyl and 1% vinyl substituents.

The results indicate that the substituents in the TBMPS group are bulky enough to produce significantly different partition coefficients, in GLC, for the derived diastereomeric ethers, and to allow, in many instances, complete resolution of the corresponding peaks. The development of practical applications will require the design of optically stable silylation reagents: on existing evidence¹⁻³, the incorporation of vinyl, naphthyl and ferrocenyl groups may be advantageous in this respect, while consideration might be given to the use of chiral silyl hydrides which tend to have greater configurational stability than halides. Meanwhile, the reactions of TBMPBr with a variety of hydroxylic substrates are being further explored.

ACKNOWLEDGEMENTS

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